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DRUG TREATMENT IN CHILDREN WITH FOCUS ON *OFF-LABEL* DRUG USE

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ABSTRACT

There is a lack of paediatric documentation concerning efficacy and safety of many drugs, which contribute to drug use outside the terms of the product license (*off-label*). In the present thesis, four studies (I-IV), using different settings and design to evaluate pharmacological treatment in children, with focus on *off-label* drug use, is presented.

Outpatient records of purchased prescriptions were retrieved to investigate the frequency and characteristics of paediatric *off-label* prescribing (I). In Stockholm, 1.8 prescribed drugs per child were purchased in the year 2000. Every fifth drug was classified as an *off-label* prescription. The proportion of *off-label* prescriptions was highest for topical drugs, due to lack of paediatric information.

A survey of all adverse drug reaction reports to the Medical Products Agency concerning paediatric outpatients in the year 2000 was performed, to investigate the frequency of *off-label* drug prescribing (II). One hundred and twelve paediatric cases, corresponding to 158 adverse reactions were reported. One third of the reports were regarded as serious, and these were more often associated with *off-label* drug prescribing. Antiasthmatic drugs were most commonly reported. Psychiatric symptoms were the most commonly reported adverse drug reactions.

Paediatric questions and answers to a Drug Information Centre in Stockholm were retrieved and analysed regarding *off-label* drug use and paediatric literature information adding to the labelling of the drug (III). During a 10-year period, 249 paediatric questions were handled. Every third question concerned *off-label* treatment, often concerning psychotropic drugs. In every other response to *off-label* questions, additional paediatric documentation concerning the drug was found in the literature.

In a prospective, nation-wide, cross-sectional study, paediatric prescriptions and *off-label* drug use to children at hospitals in Sweden were analysed (IV). Enrolment of more than 200 hospital departments resulted in data from 2947 paediatric patients, that received altogether 11294 prescriptions within two two-day-periods in 2008. Half of all administered prescriptions concerned either *off-label* drug use or unlicensed or extemporaneously prepared drugs. Paracetamol was the most common drug used both on- and *off-label*. Absence of paediatric information was the main reason for the large proportion of *off-label* prescribing of carbohydrates and electrolytes in hospitals.

This thesis has demonstrated substantial *off-label* prescribing to children in both primary and hospital health care. A common reason for this is the lack of paediatric documentation. Children have the same right as adults to well documented and safe drug therapy. Therefore, it is necessary to improve paediatric documentation through harmonization of existing scientific knowledge and clinical experience, improved structure of SPC information, and more appropriate administration forms. Furthermore, the documentation of drug treatment and its outcomes, including the reporting of adverse drug reactions, need to be improved.

Keywords: Child, drug treatment, *off-label*, drug related problems, adverse drug reactions, drug labelling

SAMMANFATTNING (SUMMARY IN SWEDISH)

Dokumentation om effekt och säkerhet av läkemedel till barn saknas ofta, vilket medför att barn förskrivs läkemedel utanför den godkända produktinformationen (*off-label*).

I denna avhandling presenteras fyra olika studier (I-IV) med olika bakgrundsdata och design för att utvärdera läkemedelsbehandling till barn, med fokus på läkemedelsbehandling *off-label*.

Expedierade läkemedel i primärvården analyserades för att identifiera hur vanligt förekommande *off-label* förskrivning av läkemedel till barn är i öppenvården (I). År 2000 expedierades 1.8 läkemedel per barn i Stockholm. Vart femte läkemedel förskrevs *off-label* och andelen var störst för topikala läkemedel, framför allt på grund av avsaknad av pediatrik dokumentation.

Biverkningsrapporter till läkemedelsverket analyserades avseende frekvensen *off-label* förskrivning (II). Under 2000 inkom 112 rapporter, omfattande totalt 158 biverkningsymtom, som gällde barn i primärvården. En tredjedel av rapporterna klassades som allvarliga och förekomsten av läkemedel förskrivna *off-label* var större bland dessa än bland de mindre allvarliga rapporterna. Psykiatriska biverkningar, respektive biverkningar av astmaläkemedel, var vanligast bland rapporterna.

Frågor om pediatrik läkemedelsbehandling besvarade vid en läkemedelsinformationscentral studerades för att identifiera läkemedelsbehandling *off-label* och kartlägga tillgängligheten av dokumentation rörande barn och läkemedelsbehandling, utöver befintlig produktinformation (III).

Läkemedelsinformationscentralen hade under en 10-årsperiod handlagt 249 frågor gällande barn. Var tredje fråga klassificerades som *off-label*, bland vilka psykofarmaka var vanligast. Dokumentation om läkemedels effekt och säkerhet på barn utöver den svenska produktinformationen återfanns i hälften av alla svar till frågor klassade som *off-label*.

I en nationell, prospektiv tvärsnittsstudie undersöktes läkemedelsordinationer, on- och *off-label*, till barn på sjukhus i Sverige (IV) under två tvådagarsperioder 2008. Över 200 sjukhuskliniker rapporterade in data från 2947 vårdade barn, som erhållit totalt 11294 ordinationer. Hälften av alla ordinationerna klassades som antingen *off-label*, licensläkemedel, eller läkemedel producerade *ex tempore* på apotek. Paracetamol var det vanligaste förskrivna läkemedlet både i enlighet med produktinformationen och *off-label*. Avsaknad av pediatrik dokumentation var den vanligaste anledningen till *off-label* förskrivning för glukos och elektrolytlösningar.

Off-label förskrivning till barn är frekvent förekommande både i primärvården och i slutenvård och vanligast anledning är att det saknas dokumentation för användning hos barn. Barn har samma rätt till väldokumenterade och säkra läkemedel som vuxna, varför det är nödvändigt att förbättra den pediatrika dokumentation. Detta kan ske dels genom att harmonisera existerande vetenskaplig kunskap och klinisk erfarenhet med produktinformationen och genom att strukturera dessa texter på ett bättre och mer ensartad sätt. Det behövs och ett bättre utbud av lämpliga beredningsformer för barn, samt en generellt bättre dokumentation av barns läkemedelsbehandling, inklusive en ökad spontanrapportering av biverkningar.

LIST OF PUBLICATIONS

The present doctoral thesis is based on the following publications and manuscripts, which will be referred to in the text by their Roman numerals, **I-IV**.

- I.** Ufer M, Rane A, Karlsson Å, Kimland E, Bergman U. Widespread *off-label* prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm. Eur J Clin Pharmacol 2003;**58**:779-783.
- II.** Ufer M, Kimland E, Bergman U. Adverse drug reactions and *off-label* prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf 2004;**13**:147-152.
- III.** Kimland E, Bergman U, Lindemalm S, Böttiger Y. Drug related problems and *off-label* drug treatment in children seen at a Drug Information Centre. Eur J Pediatr 2007;**166**:527-32.
- IV.** Kimland E, Nydert P, Odling V, Bottiger Y, Lindemalm S. Paediatric drug use with focus on *off-label* prescriptions at Swedish hospitals - a nationwide study. Manuscript.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
DIC	Drug Information Centre
DU 90%	Drug Utilization 90%
EPD	Extemporaneously prepared drugs (pharmaceuticals prepared at pharmacies)
EMA/EMA	European Medical Agency
EU	European Union
FASS	The Swedish catalogue of approved medical products
MPA	Medical Products Agency in Sweden
NA	Non applicable
OTC	Over-The-Counter (pharmaceuticals sold without prescriptions)
Q&A	Questions and answers
SD	Standard deviation
SPC	Summary of Product Characteristics
SWEDIS	SWEdis Drug Information System
WHO	World Health Organization

1 INTRODUCTION

Several years ago, the underprivileged position of children with respect to optimal drug therapies was raised, and in recent years, paediatric drug treatment and the lack of documentation in children concerning the efficacy and safety for many drugs have drawn much attention. The licensing procedure of new drugs aims at ensuring their efficacy, safety, quality and positive risk-benefit balance. This is often based on clinical trials and post marketing surveillance in adults. As a result, many drugs are neither tested, nor licensed for use in children. Several researchers have demonstrated that paediatric patients routinely are prescribed drugs in an *off-label* manner, i.e. drugs used outside the terms of the authorised product license. This *off-label* drug use means that children receive drug treatment based on less scientific documentation, which may increase the risk of drug related problems. Historically, pharmacovigilance started due to observed untoward effects in foetuses; the thalidomide disaster [1]. Despite this, documentation of paediatric drugs still remains inadequate.

Children have the same right as adults to receive safe and effective drugs, i.e. a correct drug, in a right dose, in the right way, for the right indication, for the right period of time and with correct information. Therefore, it is also important that the child's use of drugs is thoroughly documented, as well as all adverse drug reactions and other drug related problems, to ensure drug safety.

The present thesis includes four pharmacoepidemiological studies (I-IV) in children, including three retrospective register based investigations, using different sources of data, and one prospective, observational studies, all with different designs to identify and evaluate paediatric drug use, with focus on *off-label* treatment.

1.1 Children, not small adults

Treating children is different from treating adults with regard to several factors. Children are defined as all individuals from 0-18 years of age, where on one hand you

may have a premature infant that weigh only 500 mg and on the other hand a fully grown teenager, weighing 100 kg.

During childhood, from birth to adult, the body develops and grows, and it is well known that pharmacokinetic responses to a drug, i.e. drug absorption, distribution, metabolism and excretion, in a child may differ substantially from that of an adult. For example, the elimination capacity changes throughout childhood. It can be very low in the newborn, especially in the preterm neonate, due to immaturity of both the hepatic drug metabolising capacity and the kidney function, whereas the toddler and preschool child have an increased metabolic capacity and may require much higher weight-adjusted doses than adults [2, 3]. Also, the surface area-to-body weight ratio in children can be up to three times higher than in adults, which can lead to a larger proportion of absorption of topically administered drugs [4]. Suitable doses for children have often been derived by scaling from adult dosage. However, available methods do not give good enough estimates [5, 6]. Therefore, children cannot be regarded as small adults when it comes to deciding a suitable dose.

Communication is another issue that is of great importance when treating children with drugs compared to adults, where we often have to rely on the parents to receive and give information about drug treatment depending on the developmental stage of the child. Young children may be unable to swallow whole tablets (or even pieces when a tablet is crushed and blended in a fluid). Therefore, adjusted administration forms are crucial for the paediatric population [7].

1.2 Paediatric drug use

Around 100 million of the European population are children below the age of 18. In Sweden, the corresponding figure is more than two million. This group must be regarded as a substantial population with a potential need to use drugs [8]. Drug therapy is widely used to treat disease in childhood and several prescription and drug utilization studies in primary health care have shown that children, especially infants and preschoolers, receive considerable amounts of drugs [9-11].

A review including several prescription studies in outpatients showed that the prevalence of drug prescribing ranged from 51 up to 91% in certain age groups [10]. The average number of drugs prescribed per child and year was 1.1 in Sweden 2007 [12], and varied in other countries from 0.8-3.2 drugs per child per year [9, 10].

The most commonly prescribed drugs in children are antibiotics for systemic use, followed by drugs for the respiratory system and analgesics [9-11].

A few small studies have shown that children receive a substantial amount of over-the-counter (OTC) drugs and natural remedies [13-17]. Surveys estimating the overall use of OTC drugs and natural remedies in the paediatric population are lacking. Natural health products are often regarded as harmless agents. However, untoward effects have also been documented for these kinds of products [18].

Children receive considerable amounts of drugs at hospitals. However, large paediatric drug utilization studies estimating drug use in hospital care have been lacking.

1.3 Paediatric use of drugs *off-label* and unlicensed drugs

Within the present work, the term *off-label* is defined as any drug use outside the terms of the authorised product license, i.e. the summary of products characteristics (SPC). The term *unlicensed* applies to drugs that are not approved by medical regulatory authorities, e.g. the Swedish Medical Products Agency (MPA).

Drug prescribing in children has been reported to be frequently carried out in an *off-label* or unlicensed manner in hospital health care [19-29], particularly in neonatal care units [26, 28, 30-33] (*Table 1*).

Table 1: Studies of *off-label* and unlicensed drug treatment in hospital health care.

Settings	Subjects (n)	Drugs (n)	<i>Off-label</i> (%)	Unlicensed/ EPD (%)	Year	Reference
Hospital care	166	862	23	14	1996	[20]
Hospital care	609	2013	18	6	1998	[19]
Hospital care	624	2262	39	7	2000	[21]
Hospital care	132	222	26	8	2000	[22]
Hospital care	74	237	19	3	2001	[23]
Hospital care	237	2139	18	48	2001	[24]
Hospital care	1461	4265	60	NA	2002	[25]
Hospital care	60	483	25	24	2006	[27]
Hospital care	265	1450	17	NA	2008	[29]
Hospital /Neonatal care	293	1017	44	28	2002	[26]
Hospital /Neonatal care	108	628	36	13	2009	[28]
Neonatal care	70	455	10	35	1999	[30]
Neonatal care	105	525	59	16	2002	[31]
Neonatal care	97	1442	47	11	2002	[32]
Neonatal care	35	176	51	NA	2007	[33]

In hospital or neonatal care studies, the proportion of paediatric *off-label* and unlicensed drug prescriptions varies between 10-60% and 3-48%, respectively (Table 1) [19-27, 30-33].

Prior to study I, *off-label* drug use among outpatients had been poorly investigated. At the same time frame as study I, several investigations were performed in different European countries (Table 2). The proportion of *off-label* and unlicensed prescriptions varied between 11-26% and 0.3-17%, respectively [7, 34-40]

Table 2: Studies of *off-label* drug prescription in primary health care.

Settings	Subjects (n)	Drugs (n)	<i>Off-label</i> (%)	Unlicensed/ EPD (%)	Year	Reference
Outpatients	989	2522	29	4	2000	[34]
Outpatients	1175	3347	11	0.3	2000	[35]
Outpatients	455661	1592006	13	NA	2002	[36]
Outpatients	1802	1925	15	<1	2002	[37]
Outpatients	19283	68019	23	17	2002	[38]
Outpatients	6141	17453	14	15	2002	[26]
Outpatients	18043	66222	21	17	2003	[7]

Some studies regarded licensed drugs as unlicensed when the paediatric labelling in the SPC stated that the drug was not recommended for children or absence of paediatric documentation, or contraindicated for use in children [20, 24, 26, 39]. Other studies excluded certain pharmacological treatment, i.e. intravenous glucose and sodium chloride solutions [27, 28].

The most common therapeutic groups of drugs, both in primary and hospital health care, were antibiotics, analgesics and drugs for the respiratory tract [19-27].

The main reason for a drug to be classified as *off-label* was that the dose, the frequency of administration, or the age of the patient was not in agreement with the drug labelling [19-27, 38].

The proportions of *off-label* and unlicensed drug use in previous studies varies widely, both in primary (table 2) and hospital (table 1) care, which can partly be explained by the various settings of the paediatric care, e.g. single general practice or specialised unit or restrictions to a certain regional areas or a single study day. Another important source of variations is probably interpretations of the definition of *off-label* and unlicensed drug therapy, which makes it difficult to compare studies.

Extemporaneously prepared drugs (EPD) apply to drugs prepared at pharmacies and are important for the paediatric population. It is probably widely used, due to lack of proper drug forms or strengths necessary for children [41, 42]. Most studies [19-27, 30-33, 35, 38, 39, 43] regarded EPD as well as licensed drugs, modified by i.e. crushing tablets or diluting drug solution, as unlicensed drugs. Little information exists to support the pharmacokinetics of EPD and they are rarely quality assured. Thus, the background documentation of EPDs is even poorer than that of drugs used *off-label*. The proportion of EPD use, and which drugs children actually receive, is another area that is poorly investigated.

Very little has been published concerning what drugs children in Sweden actually receives, both licensed and unlicensed drugs, EPD and natural remedies, as well as the proportion of *off-label* prescriptions. A single Swedish paediatric department was included in a European study concerning *off-label* drug use, showing that 67 percent of children received at least one drug *off-label*[21]. No data concerning *off-label* use of drugs at Swedish neonatal care units or in paediatric outpatients have previously been published. *Off-label* drug treatment is mainly discussed as a paediatric issue, however, it is documented in adults as well [44].

1.4 Drug related problems and *off-label* drug treatment in children

A drug related problem has been described as an event or circumstance involving drug therapy that actually or potentially interferes with desired outcomes. Drug related problems can be divided into several categories such as adverse drug reactions or drug use/administration problems [45]. Adverse drug reactions is regarded as an unintended drug response that occurred at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease [46]

Drug related problems comprise of a broad set of clinical situations and can be difficult to analyse and validate. Most studies focus only on adverse drug reactions (ADRs), and a fewer studies do also include other types of drug related problems. Drug related problems were found to be the cause of admission to hospitals for children in three studies with an incidence between 3.4% and 7.9% [47-49]. Potential adverse drug events in hospitals have been described to be three times more common in paediatric patients compared with adults [50].

Several prospective studies indicate that ADRs in children, especially in hospitalised children, are of great clinical relevance [32, 51-53]. The overall incidence of ADRs in children in hospital care has been documented to range from a single or a few percent up to nearly one fifth of the study population [51-58]. In outpatients, between 0.5-9 % suffered from ADR [53, 59]. Serious reactions occurred in almost 40% of ADRs documented in paediatric hospital admissions [55] and accounted for about 10-12% in hospitalised children [54-57]. It has been suggested that up to one half of the documented drug related problems could have been avoided [47, 49, 60].

Although the incidence of reported ADRs in children varies, probably due to different study settings and different sizes of study populations, similar rates of ADRs have been reported in various adult populations [61-64].

A few studies have analysed the potential association between *off-label* drug use and the risk of ADRs [65-68]. In a prospective, hospital-based study (n=936), 35% of the given drugs were unlicensed or *off-label* and the incidence of ADRs was 4% among the licensed drugs and 6% among the unlicensed or *off-label* drugs [65]. Another prospective study, based on the prescribing habits of 39 participating physicians, nearly 20% of (n=1419) prescriptions to outpatients were regarded as *off-label*, and the incidence of ADRs (a total of 20 non-serious events) was about 1.4% for licensed prescriptions, compared with 2% for unlicensed or *off-label* drug prescriptions [66]. There are additionally two studies based on spontaneous ADR reports from hospital care [67, 68]. In the first study, based on 95 ADR reports, 25% of the reports concerned medicines used *off-label* [67] and in the latter study, based on 182 ADR reports, *off-label* drug use together with other incorrect use such as drug interactions was more often associated ADRs reports than drugs used in line with the product labelling [68].

Medication errors, e.g. a drug given in an improper or unintended dose or route, are another area in paediatric health care of great importance [69, 70]. However, this issue will not be addressed within the present work.

Long-term pharmacovigilance studies, especially focusing on the impact of *off-label* drug use and drug related problems, are still missing in the paediatric population.

1.5 Documentation of paediatric drug use

During the last years efforts have been made through regulatory authorities to improve knowledge on paediatric drug therapy. As a consequence of the previous lack of paediatric data on medicinal products, a new legislation was introduced into the European Union in 2007 [71]. The new Paediatric Regulation aims to facilitate the development and availability of medicines for children, to ensure that those medicines are of high quality, ethically researched, and authorised appropriately and to improve the availability of information on the use of medicines for children. All this shall be achieved without subjecting children to unnecessary trials, or delaying the authorisation of medicinal products in adults. An analysis of at that time new drugs with marketing authorization revealed that among 45 new substances, 29 were of possible use in children, only 10 were licensed for paediatric use [72]

Drug Information Centres (DICs), are established both in Europe and the United States [73-75], where evaluated drug information, similar to clinical consultations, for adults as well as for paediatric patients can be attained. In Sweden, the first centre was started at the Department of Clinical Pharmacology at Huddinge Hospital in Stockholm in 1974, through cooperation between clinical pharmacologists and information pharmacists. Today, this is one out of six regional DICs in Sweden [76]. The DIC in Stockholm receives about 1000 questions per year, mainly concerning ADRs, drug interactions, drugs during pregnancy and breast-feeding and drug choice or dosing [73].

No published study on paediatric drug treatment based on data from a DIC has been found, but there are three retrospective DIC-based analyses concerning the use of drugs during pregnancy or breast-feeding supporting DIC as an important source of evidence based information [77-79].

Inadequate labelling of paediatric drugs is often assumed to be due to the lack of scientific documentation in children. However, it has not been investigated to what extent available literature information concerning paediatric drug efficacy and safety outside the SPCs actually exists. Neither has it been studied how well a child's actual drug use, licensed or unlicensed drug treatment nor EPD and natural remedies, are documented in the e.g. the medical records.

2 AIMS OF THE THESIS

The main aim of this thesis has been to use an epidemiologic approach to describe different aspects of paediatric drug treatment today, as a basis for the guidance of further clinical studies, aimed at approving the documentation of the safety and efficacy of drug treatment to children.

This main aim can be divided into the following, separate aims:

- To investigate and characterise drug prescribing to children in Sweden, in primary health care, as well as in hospital care, and to analyse the extent and manner of *off-label* and unlicensed paediatric drug use in therapeutic areas.
- To investigate clinical aspects of paediatric *off-label* drug treatment by
 - a) characterising ADR reports concerning paediatric outpatients, including the proportion of both serious and non-serious ADR reports related to *off-label* drug prescribing.
 - b) analysing paediatric Questions and Answers at a Drug Information Centre regarding drug related problems and *off-label* drug treatment.
- To analyse the availability of documented information, adding to the information of the paediatric labelling of drugs, in relation to paediatric drug related problems, as presented to a Drug Information Centre.

3 MATERIALS AND METHODS

3.1 Settings and subjects

Paper I:

This is a retrospective analysis of pharmacy-dispensed drugs to children and adolescents regarding *off-label* prescriptions in the year 2000. A computerised population-based prescription database produced by the National Corporation of Swedish Pharmacies was used to analyse drug prescriptions to children less than 16 years of age. In Sweden no prescription data could be individually linked at the time of the study. Therefore, the data have been analysed on an aggregated level.

The drugs were ranked by purchased volume according to the number of prescribed items. The analysis was restricted to the Drug Utilisation 90% segment (DU90%) containing those drugs that accounted for 90% of the total number of prescriptions [80]. *Off-label* drug prescribing was assessed with respect to age, formulation and route of administration. The *off-label* assessment was validated through the independent analysis of a random sample of 50 different brand names by another researcher, and was found to be identical with the initial assessment.

Furthermore, adherence assessment to regional guidelines was performed using the list of recommended drugs (The Wise Drug List) from the local Drug and Therapeutic Committee in Stockholm County [81].

Paper II:

Study **II** consists of a nation-wide survey of spontaneous ADR reports to the Medical Products Agency (MPA) in Sweden. The extent and characteristics of *off-label* prescribing were assessed among drugs included in the ADR reports. The SWedish Drug Information System (SWEDIS) produced by the MPA was used to identify all reported ADRs in children or adolescents under the age of 16 during year 2000. Data collection and evaluation of the ADR reports are performed by the six regional pharmacovigilance centres.

An ADR was defined according to the World Health Organization (WHO) [46]. *Off-label* drug treatment was assessed on the basis of age, dose, indication, formulation, route and frequency of administration. ADR analysis and *off-label* assessment were

independently performed by two researchers and found to be identical. Population and aggregated drug utilization data were obtained from Statistics in Sweden [8] and the National Corporation of Swedish Pharmacies [82], respectively.

A total of 444 ADR reports concerning children and adolescents younger than 16 years in Sweden were identified in the year 2000. Vaccines given to children are almost all licensed and labelled for use in the paediatric population and therefore, they were not included in the further analysis (n=308). Of the remaining 135 ADR reports, another 24 reports were excluded for the following reasons: inpatients, newborns suffering from an ADR due to maternal drug treatment, unclassifiable causality, and OTC drug use.

Paper III:

All documented questions and answers (Q&A) handled by the DIC at Karolinska University Hospital-Huddinge, Sweden were used in this study. The Q&A are continuously registered in a local database, which also contains information concerning demographic data, drug and medical history of the patient, type of drug related problem and literature sources used.

All Q&A during a ten-year period, from 1995 to 2004, were retrieved and systematically analysed. Out of a total of 6842 questions processed at the DIC from 1995 to 2004, 300 (4,4%) were documented to concern children. Analysis was restricted to questions concerning children less than 16 years of age. In total, 51 (17%) of the questions were excluded from further analysis as the question concerned: *breast-feeding and/or pregnancy, patients 16 years or older, food, chemicals or doping substances, accidental ingestion of drugs, or multiple registration of the same question*. Q&A were classified regarded *off-label* drug use and further analysed with respect to their content of evaluated literature information, adding to the information given in the labelling of the drugs in the SPC in the Swedish catalogue of medical products [83].

Paper IV:

All identified paediatric hospital departments, as well as a number of other departments that treat paediatric patients (e.g. departments of radiology and ear, nose and throat diseases), in Sweden were enrolled in this study. All 44 participating hospitals

received written and oral information about the design and purpose of the study at several meetings, and special prescription forms were distributed by mail prior to the study periods.

Data on concurrent drug prescriptions to paediatric patients in hospital care were collected during 48 hours in the middle of May and October 2008, respectively, by the treating nurses and/or physicians. The prescription form requested information about patient social security number, age, gender, weight and cause of hospital admittance, as well as name of the drugs, indication, strength, dosage, form and route of administration, and estimated duration of drug treatment. Furthermore, the questionnaire requested information on whether the drug was used for the treatment or prevention of disease or for diagnostic purposes. Only patients 18 years of age or less who received any drug treatment were included in the final analysis.

Data were entered and analysed in a database (Microsoft Access 2000). Data lacking in fields, such as route of administration, formulation, duration of treatment and cause of treatment, were classified as unknown unless it was clearly described elsewhere in the prescription form.

The *off label* analysis was performed for each prescription of a licensed drug. The *off-label* assessment was validated through an independent analysis of a random sample of 20 percent of the different pharmaceutical compounds by a hospital pharmacist, and was found to be in accordance with the initial *off-label* analysis.

To investigate the external validity of the data, information concerning all paediatric hospital admissions during the two study periods was retrieved from the *National in-hospital patient register* from the National Board of Health and Welfare (Socialstyrelsen) [12].

3.2 Classification

3.2.1 Drugs (Paper I-V) and treatment guidelines (Paper I)

Licensed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification to the fifth level [84] and their license status was determined by

the SPC from the Swedish catalogue of approved medical products (FASS) as the primary reference source in studies **I-IV** [83]. A book with extemporaneously prepared drugs [85] (**I,II,IV**), contact with the manufacturer (**I,II**) or product information provided by the MPA homepage (**I-IV**) was used as secondary reference sources. In the first (**I**) and second study (**II**) FASS for the year 2000 was used, in the third study (**III**) FASS corresponding to the year of the questions and in the last study (**V**) SPC available online in the year 2008 was used. All drugs that were not listed in our primary or secondary reference sources mentioned above were regarded as unlicensed.

3.2.2 Age groups (Study V)

In study **IV** the paediatric patients were divided into four different age groups: *neonates (0-28 days), infants (1-23 months), children (2-11 years) and adolescents (12-18 years)*. This was done in accordance with guidelines from the European Medicines Agency (EMA), with the exception that premature neonates were included in the neonatal group [86].

3.2.3 Adverse drug reactions and other drug related problems (Paper II-III)

In study **II**, each reported ADR was classified with respect to causality and seriousness. The level of causality was restricted to certain, probable or possible, using the WHO definitions [46]. We also classified each ADR as a type A (pharmacological) or type B (idiosyncratic) reaction.

In study **III**, five different categories of drug related problems were used; *ADR, drug interactions, drug kinetics, drug choice and/or dosing, drug formulation and/or administration*, depending on the main objective of the DIC question [73, 76].

3.2.4 Off-label drug treatment (Paper I-IV)

The *off-label* assessment was performed in the studies **I-IV** by analysing the license information for included drugs with the reference sources mentioned above (see 3.2.1). Sections 4.1, 4.2, 4.3 and 4.4 of the SPC, which concern indications, dosages and way of administration, contraindications and warnings, were used to assess the

off-label status of prescribed licensed drugs. Also, a search for the terms “child/children” was performed on the complete SPC text. The term *off-label* was defined as any drug use outside the terms of the product license.

Off-label prescriptions were further divided into seven different categories as shown in table 3.

Table 3: Descriptions of *off-label* categories

<i>Off-label category</i>	Description	Paper
<i>Age</i>	Drug not recommended for a certain age-group in the SPC	I-IV
<i>Weight</i>	Drug not recommended for children below a certain weight in the SPC	I-II,IV
<i>Absence of paediatric information</i>	Information of drug treatment to paediatric patients (less than 16 years of age) is not mentioned at all in the SPC	I-IV
<i>Lack of paediatric clinical data/trials</i>	Stated lack of scientific data or clinical studies on drug efficacy and safety for paediatric patients (less than 16 years of age) in the SPC	I-IV
<i>Contraindicated</i>	Drugs stated in the SPC to be contraindicated in children	I-IV
<i>Indications</i>	Drugs prescribed for indications not listed in the SPC	II-IV
<i>Administration route</i>	Drugs administered by a route not approved according to the SPC	I-II,IV

Product information allowing paediatric use in general, without any age or dose specification, was regarded as on-label in paper **I-III** but rendered the prescribed drug an *off-label* status if given to patients less than 1 year of age in paper **IV**. This definition is based on the fact that there are well known age dependent differences in the pharmacological response to drugs and drug kinetics, especially in neonates and infants less than 1 year. A single prescription could be regarded as *off-label* in more than one category.

In study **II**, drugs that exceeded a recommended dose by more than 20% were regarded as *off-label*, but not drugs given in less than the recommended dose.

3.2.5 Documentation of drug treatment in children (Paper III)

In study **III** the content of evaluated literature information, adding to the labelling of the drugs, was assessed and categorised for all Q&As regarded as *off-label* drug treatment. Four different categories of information were used as shown in table 4.

Table 4: Definition of categories of type of information.

<i>Category</i>	<i>Type of information</i>
<i>Age</i>	Age requirements for paediatric drug treatment
<i>Dosing</i>	Paediatric dosing recommendations
<i>ADRs</i>	ADRs not mentioned in the labelling of the drug
<i>Drug interactions</i>	Drug interactions not mentioned in the labelling of the drug

3.3 Ethical considerations

None of the registers used in study **I-III** contained any references to patient identity and therefore no ethical approval was needed for these studies. Study **IV** was approved by the Research Ethics Committee at Karolinska Institutet, Stockholm, no 2008/502-31/2.

4 RESULTS

The results are summarised in this section. For a more complete account see the separate publications **I-IV** (Appendix).

4.1 Drug treatment (Paper I-IV)

There was a substantial use of drugs among children in all studies (**I-IV**) with an average use of 1.5-1.8 prescribed drugs per child in outpatients (**I,II**) and 3.8 drugs per child in hospital care (**IV**) as shown in table 5

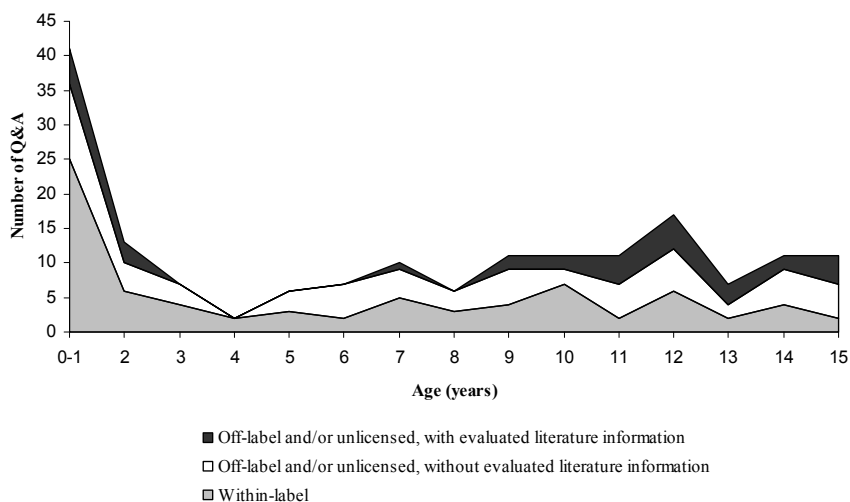
Table 5 Drug use and off-label proportion in Paper I-IV.

Study	Subjects (n)	Drugs (n)	Median age (years)	Off-label (%)	Timeframe	Setting
I	357 784	575 526	7	21	Year 2000	Prescriptions in primary health care
II	112	125	7	42	Year 2000	ADRs reports from primary health care
III	249	298	NA	31	1995-2004	Q&A from a DIC
IV	2947	11294	4	41	4 days 2008	Prospective cross-sectional study in Hospital care

(NA - not applicable)

Children less than two years of age is an age group that receives a substantial amount of drugs as illustrated in Figure 1 (**III**) and Table 6 (**IV**). In primary care, the median age of children is higher, as shown in Table 5.

Figure 1 (Paper III): Number of questions and answers classified as within-label, *off-label* and/or unlicensed with or without evaluated literature information, adding to the labelling of the drugs at a Drug information centre.



(n=172 questions with known age)

Table 6 (Paper IV): Distribution of prescriptions of licensed drugs, unlicensed drugs, extemporaneously prepared drugs and undocumented use of drugs by age groups in children at hospitals.

Age groups	Patients	Prescriptions	Licensed	Unlicensed	EPD	Undocumented
All	2947	11294	9471	516	1177	5608
Median (SD)	NA	3 (3.7)	2 (3.2)	1 (1.3)	1 (1.2)	2 (2.5)
Neonates	476	1875	1271 (68)	139 (7.4)	428 (23)	1310 (70)
Infants	698	2644	2134 (81)	132 (5.0)	320 (12)	1505 (57)
Children	1043	3800	3378 (89)	130 (3.4)	274 (7.2)	1789 (47)
Adolescents	730	2975	2688 (90)	115 (3.9)	155 (5.2)	1011 (38)

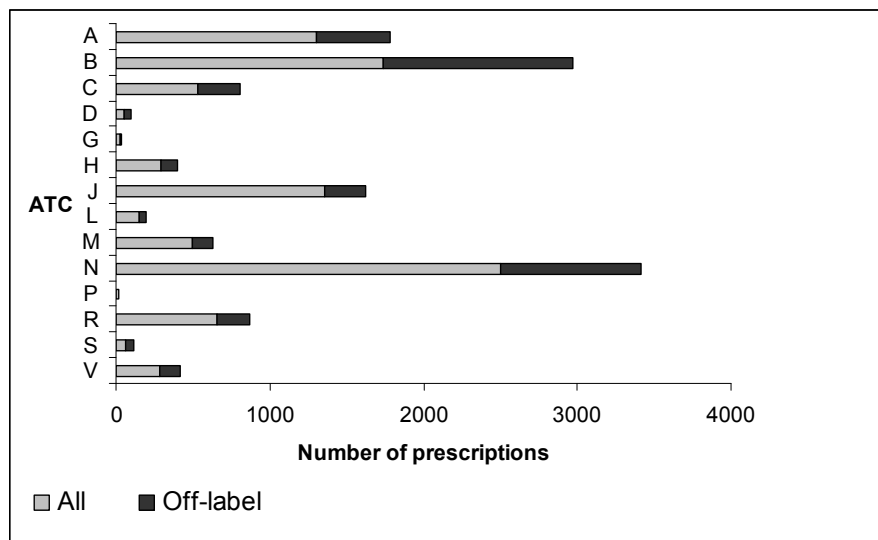
Infants and neonates received more than half of all prescriptions for a longer duration than one week, whereas children and adolescents received 74% of all prescriptions given as a single dose or on demand medication in study **IV**.

Antibacterials for systemic use (i.e. phenoxymethylpenicillin, trimethoprim) and anti-asthmatics (i.e. budesonide, terbutalin, salbutamol) were found to be the most commonly prescribed drugs to outpatients in paper **I**, which is in agreement with previous findings [9, 10]. In study **III**, the most common drugs in the DIC questions were antibacterials for systemic use (erythromycin, pivmecillinam), followed by antiepileptics (carbamazepine, valproate). Intravenous carbohydrates or electrolytes solutions (ATC B) as well as analgesic agents (ATC N), e.g. paracetamol and morphine, were commonly prescribed drugs among children at hospitals in paper **IV** (Figure 3). In paper **IV** the paediatric patients had been prescribed five percent unlicensed drugs and 10 % EPD (Table 6).

Among the ADR reports in the second study (**II**) and among the DIC questions (**III**), almost all drugs were systemically administered.

The most frequently prescribed licensed drug groups, classified according to ATC-codes in paediatric patients at hospitals (**IV**) were drugs for the nervous system (N), drugs for blood or blood forming organs (B) and drugs for infections (J) (Figure 2).

Figure 2 (Paper IV): Distribution of prescriptions of licensed drugs and *off-label* drugs for the main ATC subgroups in paediatric patients at hospitals. (See also Table 7)



In paper **III**, 24% of the Q&A concerned unlicensed drugs or herbal remedies.

Among EPDs, intravenous morphine, followed by intravenous caffeine and oral salt formulations were most common (**IV**). The most common unlicensed drugs were multivitamins and allergen extracts (**IV**).

In paper **IV**, the age group of children (2-11 years) received the highest proportion of licensed drug prescriptions, whereas neonates (0-28 days) and infants (1-23 months) were given the highest proportion of EPDs and unlicensed drug prescriptions (Table 6). Neonates and infants received 53% of all unlicensed prescriptions and 64% of all EPD prescriptions (Table 6).

4.2 *Off-label* drug use (Paper I-IV)

Off-label drug treatment in children was the main topic of interest for all of the papers **I-IV**. More than one fifth of prescribed drugs for all age groups were classified as *off-label* in paper **I**, and this proportion was even higher among outpatients in ADR reports

(II). In the third study (III), we found that more than every third question to the DIC concerned *off-label* drug treatment (Table 5). In study IV the *off-label* proportion was more than 40%. Every other prescription to a child in a Swedish hospital was classified either *off-label* or an EPD or an unlicensed drug.

The proportion of *off-label* drug use was highest among adolescents (12-15 years) in study I (29%) and III, whereas in study IV, it was highest for neonates and infants (Table 6).

The proportion of drugs used *off-label* varied considerably between therapeutic groups and between the different studies. The proportion of *off-label* drug prescriptions in outpatients (I), was found to constitute more than 70% of dermatological drugs (e.g. *hydrocortisone*, *fucidid acid*). In the ADR reports (II) *off-label* drug use was most common among drugs for the respiratory system (e.g. *montelukast*, *budesonide*). Among paediatric Q&A from a DIC, *off-label* drug use was most common among drugs for the nervous system (e.g. *risperidone*, *selective serotonin reuptake inhibitors*) (III).

Among paediatric patients in hospital care (IV) drugs for the blood and blood forming organs (e.g. *carbohydrates and/or electrolyte solutions*), the nervous system (e.g. *paracetamol*, *morphine*, *midazolam*) as well as drugs for the alimentary tract and metabolism (e.g. *docusate sodium*, *potassium citrate*, *eso- omeprazole*) had the highest number of *off-label* prescriptions. Other drugs with a high clinical important proportion of *off-label* drug use were found (IV), e.g. drugs used for cardiovascular diseases and different allergy tests (table 7).

Table 7: The most commonly prescribed licensed substances (Rx (no)-number of prescriptions) used in an *off label* manner (n=3905) in each ATC group in paediatric patients at hospitals (IV).

ATC	Rx (no)	<i>Off-label</i> (%)	Most common substances
A	1306	37	Docusate sodium, potassium citrate, eso- omeprazole
B	1736	71	Carbohydrates, electrolytes
C	531	53	Epinephrine, furosemide, clonidine
D	54	83	Tar like, hydrocortisone/miconazole
G	23	61	Magnesium hydroxide, sildenafil
H	291	38	Prednisolone, betamethason
J	1360	19	Sulfamethoxazole/trimetoprim, ampicillin
L	155	28	Azathioprine, etoposide
M	494	27	Diclofenac, ibuprofen
N	2503	36	Paracetamol, morphine, midazolam
P	19	5	Pentamidine isethionate
R	660	32	Budesonide, salbutamol
S	59	92	Chloramphenicol, fusidic acid
V	280	49	Different allergy tests

The main reasons for drug use in an *off-label* manner in nearly all studies (I,II,IV) was found to be lack of paediatric labelling, rather than explicit prohibitions of paediatric use, followed by a non-approved dose in relation to age or weight in study II and IV. Lack of paediatric drug labelling was found for several drug groups, such as topically administered drugs in paper I, and in paper IV for carbohydrates and electrolytes, analgesic drugs, laxatives and proton pumps inhibitors.

In study IV, five percent of all the prescriptions were administered in a way not in agreement with the intended route of administration. The most frequent aberrant route

of administration was the use of an intravenous drug formulation for oral administration (carbohydrates, electrolytes, midazolam) or inhalation (epinephrine).

4.3 Drug related problems (II-III)

Off-label drug prescribing in study **II** were more often associated with serious (51%) than non-serious (39%) ADR reports, and reported ADRs were three times as often classified as type B (idiosyncratic) than type A (pharmacological) reactions.

In paper **III**, adverse drug reactions and drug choice or dosing in children were most common in the DIC Q&A (Table 8).

Table 8: Proportion of drug related problems, *off-label* drug treatment and evaluated literature information, in addition to the labelling of the drugs, in Q&A to a DIC.

Drug related problem	All [n (%)]	<i>Off-label</i> [n (%)]	Literature information [n (%)]
<i>All</i>	249 (100)	78 (31)	41 (16)
<i>Adverse drug reactions</i>	91 (37)	20 (26)	8 (20)
<i>Paediatric drug choice and dosing</i>	85 (34)	31 (40)	21 (51)
<i>Drug interactions</i>	31 (12)	9 (12)	6 (15)
<i>Drug formulation and administration</i>	25 (10)	5 (6)	1 (2)
<i>Paediatric drug kinetics</i>	17 (7)	6 (8)	5 (12)

Among the most common ADRs, in ADR reports (paper **II**) and/or Q&A (paper **III**) from a DIC, were symptoms from the central nervous system, skin reactions, gastrointestinal, and haematological symptoms (Table 9).

Table 9: Numbers and proportions of the most common kinds of ADRs in study II and III.

Adverse drug reactions	Study II [n (%)]	Study III [n (%)]
All	158 (100)	91 (100)
Central nervous system disorders (sleeping disorders, aggressiveness, headache, paresthesia)	54 (34)	17 (19)
Skin reactions, allergic reactions (urticaria, exanthema, allergy)	29 (18)	14 (15)
Gastrointestinal symptoms (nausea, vomiting, abdominal pain)	19 (12)	3 (3)
Hematological symptoms (leucopenia, thrombocytopenia, bleeding complication)	14 (9)	14 (15)
Systemic inflammatory reactions (meningitis, pancreatitis)	13 (8)	9 (10)
Miscellaneous (abuse, adverse effects of the eye and respiratory tract)	29 (18)	34 (37)

4.4 Pediatric documentation of drug treatment (I,III)

In the third study (III), more than half of the answers to *off-label* questions were found to contain evaluated paediatric drug information, that added to the information of the SPC. Mostly, additional information concerning drug choice or dosing was found (Table 8). Scientific papers from medical databases, e.g. PubMed, and medical handbooks were the most common sources for paediatric documentation, which consisted mainly of documentation of treatment concerning paediatric age requirements and dose recommendations.

Within the DU90% segment, 61% of prescription items in study I corresponded to drugs that were recommended in the local treatment guidelines.

5 DISCUSSION

5.1 *Off-label* drug treatment

5.1.1 Some clinical aspects

This thesis confirms that paediatric patients, both in primary and hospital health care, are subject to a large proportion of drug treatment that is not approved by regulatory authorities, meaning that the safety and efficacy of this drug treatment is neither well studied, nor sufficiently documented. *Off-label* drug treatment is, however, a multifaceted concept that may be of different clinical importance in different treatment situations. For example, the proportion of *off-label* drug use is apparently higher in hospitals than in primary health care, whereas primary health care involves a larger population of children under less intense medical supervision.

The highest *off-label* drug use in paediatric hospital care consisted of intravenous carbohydrates and electrolytes, given orally to neonates and infants. From a purely pharmacological point of view, this treatment, based on long time clinical experience, probably represents minimal risks and the benefits are quite clear. On the other hand, to administer drugs by an unintended route may be associated with a high risk for administration errors.

Neonates, in particular, and infants have a substantial *off-label* drug use, as well as the highest use of EPDs and unlicensed drugs in hospital care. Since neonates and infants are particularly vulnerable, due to their immature renal and hepatic function, as well as body proportions, difficulties in drug administration and ability to express adverse drug reactions, further evidence of both safety and efficacy of drugs is urgently needed in these age groups. The margins when a wrong dosage is given are smaller for young children compared to adults.

Adolescents were frequently prescribed *off-label* drugs in primary health care and probably receive doses similar to that of the adults. However, it has been shown that adolescents can have other patterns of adverse drug reactions to e.g. antidepressive agents [53], indicating that adolescents have another sensibility to drugs than adults, despite having approximately the same body size.

Drugs administered topically to children were often classified as *off-label* in the studies of this thesis, both in hospital and primary health care. The reason for the *off-label* classification is mainly lack of paediatric information in the drug label, although a large clinical experience of topical drug treatment exists. The fact that only few ADR reports concern topically administered drugs may partly be due to a belief among prescribers that these drugs have a lower propensity to cause ADRs, than do systemically administered drugs. However, children do have a higher surface to body weight ratio than adults, and it has been observed that e.g. topically administered tacrolimus can give rise to high blood concentrations in children [87]. The potential risks of specific topical drugs, like e.g. immunosuppressants, need to be further studied, and drug labelling needs to be improved. Topically administered drugs in general, however, should perhaps not be regarded as the most prioritized drugs for further studies.

5.1.2 Antipyretics and analgesics

Paracetamol is, according to these studies, the most commonly used drug to treat fever and pain in children in primary health care, with or without a prescription, as well as in hospital care. Still, the *off-label* use of paracetamol is substantial, mainly due to *off-label* classification for age or weight, i.e. the drug was given to a child younger or smaller than specified in the dosage recommendations. This can partly be explained by unclear age definitions in the SPC. Although paracetamol is generally considered safe in paediatric care, a previous Cochrane review pointed out that there is limited evidence regarding the efficacy and safety for paracetamol in the treatment of fever in children [88].

Other analgesics, such as opioids or diclofenac, have been highlighted by others in the past [19-21, 24, 30, 32, 36, 89] and by us, as areas where clinical trials appear to be needed to obtain appropriate dosages for all age groups and better paediatric drug labelling. Analgesics have also been listed on the EMAs priority list of paediatric drugs to be further studied [90].

5.1.3 Galenic aspects

The high rate of use of EPDs, unlicensed drugs or drugs administered *off-label* strongly supports the need for improvement by the manufacturers in providing

appropriate and approved galenic preparations suitable for children of different size and age [19, 22, 25]. Examples of very commonly used drugs that are lacking appropriate dosage forms include caffeine citrate oral solutions, intravenous morphine solution 1mg/ml and 0.05mg/ml, and the oral vitamin solution, Protovit®, used in neonatal and infant care, that was withdrawn in 1989 due to low sales numbers and is now only available as an unlicensed drug [91]. Drugs and Therapeutic Committees may play a role here, in promoting the use of drugs that are available in dose sizes or forms that are suitable also for paediatric use.

5.1.4 The paediatric drug label

Lack of paediatric labelling was one of the most common reasons for *off-label* drug use in nearly all of the studies (paper **I,III,IV**) presented in this thesis. However, we found that additional documentation concerning paediatric use, outside the drug label of the SPC, was often available via e.g. Pubmed. One reason for paediatric *off-label* drug treatment is therefore the lack of harmonisation between paediatric documentation in the existing literature evidence and the authorised drug label. It is not feasible for all physicians responsible for paediatric prescribing to conduct Pubmed literature searches themselves every time they prescribe a drug *off-label*. They need of readily available, processed, evaluated and continuously updated information. In individual patient cases, this can obviously be provided by the DICs. However, there is also a need for expert groups devoted to paediatric drug treatment within the organisation of the Drug and Therapeutic Committees, which could continuously process new literature data and convey relevant information to physicians in both hospital and primary health care. Such a group has now been implemented in the work of the Drug and Therapeutic Committee of Stockholm County Council.

5.1.5 Drug related problems

Use of drugs in an *off-label* manner have been shown, by us and by others, to be more often associated with ADRs than drugs used according to the SPC [29, 65-68]. Whether this finding is significant or generalizable to all *off-label* drug use is not possible to determine.

In one study presented in this thesis, reported ADRs in children were more often idiosyncratic (type B) than due to the known, pharmacological action of the drug (type A). This is true for all spontaneous ADR reporting, also in adults. However, it is not known if the true incidence of type B reactions is higher in paediatric patients compared with adults.

While licensed drugs are monitored by epidemiological surveys and post marketing studies of safety, there is currently no clear process for collecting information on ADRs for EDP or unlicensed drugs. Therefore spontaneous reporting of ADRs can be the only way of discovering hazardous effects, even though it is well known that the spontaneous reporting system is subject to substantial under-reporting [92, 93]. The annual reporting rate for non-vaccine related reports in Sweden is approximately the same today, as in the year of 2000, when study II was performed.

The drug related problems presented in the questions to the Drug Information Centre in study III did not always relate to past events. Sometimes the questioner asked prior to prescribing a drug. The DIC service can thus hopefully be of aid in preventing some drug related problems in children. It has been shown that the DIC has a cost-saving potential in preventing ADRs in general [94].

5.2 Documentation of paediatric drug treatment in health care

It has been shown that physicians are well aware of the lack of paediatric labelling [95]. One reason for treatment with drugs in an *off-label* manner is probably that paediatricians have clinical experience that supports *off-label* drug use. Even so, all drug treatment, including the use of drugs in an *off-label* manner, needs to be thoroughly documented in the medical record of the patient.

With the development of electronic, computerized patient record systems, structured documentation of *off-label* and unlicensed drug use, including the clinical outcomes of such treatment, could greatly improve the knowledge in this area. There are, however, some obstacles to this development. For example, some electronic record systems are not designed to document drug treatment in a structured way. Even today,

many systems lack a separate “drug treatment module”, and existing such modules may not be well suited for the documentation of paediatric drug use.

Furthermore, health care personnel are not always very good at collecting relevant information concerning drug use, and this may be especially true in the treatment of children, in whom drug treatment may not be in focus. According to our own, unpublished data, less than half of the drugs used by 272 children prior to visiting an emergency room at the Karolinska University Hospital, were documented in the medical record. According to a structured and validated questionnaire, answered by patients/guardians in the waiting room, 40 percent of the children had used at least one prescribed drug, 65 percent had used at least one OTC drug and 8 percent had used natural remedies or alternative medicines before visiting the emergency room.

Looking into the medical records from the visits, the heading “Medicines” was found in only 28 percent of the records. Information concerning use of drugs, OTC, or complementary medicine, ongoing or prior to the visit to the emergency room was, however, mentioned in the text in 58 percent of the records. In more than half (54 %) of the patients’ records, there was at least one drug missing, compared with the information in the questionnaire. More than two-thirds of the missing medicines were OTC drugs and only nine of the 22 different natural remedies were documented in the medical records (table 10).

Table 10: Drugs use prior to visiting the hospital as documented from a questionnaire answered by 272 patients/guardians in the paediatric emergency waiting room and in the medical records from the same visit.

	Number of drugs in the questionnaire	Percent of drugs missing in the medical records
All	458	51%
Prescribed drugs	182	29%
OTC	254	65%
Natural products	22	77%

5.3 Some methodological considerations

Comparison of our data with studies in other countries regarding the proportion of *off-label* prescribing and reason for *off-label* drug use is difficult due to a high variety of settings, small datasets and varying definition of *off-label* status among previously published studies in this field. The definition of *off-label* treatment needs to be clarified and standardized in order to be able to compare data in future studies.

In primary health care, one fifth of the prescription was classified as *off-label*, which may not be a high number, particularly if topical drugs are excluded. The use of fewer *off-label* categories probably results in an underestimation of the *off-label* proportion. The reason for using different *off-label* categories is often due to limitations in the available data. In study **I** and **III**, for example, a dose assessment was not possible, since the dose was not known at all in the study **I** and only in a few questions in study **III**. If we had been able to analyse the dose in relation to the *off-label* assessment in study **I**, the *off-label* proportion might have been higher due to either too low or too high paediatric doses [96].

In our first study (**I**) we focused on those drugs accounting for 90% of the prescription (DU90%) for practical reasons. The remaining 10% of the drugs prescribed are used more rarely and perhaps even more often lack paediatric labelling. Therefore, use of DU90% in this study could have contributed to an underestimation of the *off-label* proportion of outpatient drug prescribing. In future studies it would be of greater interest to investigate all prescribed drugs.

In paper **IV** the data collection depended on the work by attending paediatric hospital care professionals, and the vast majority of prescription forms appeared to be carefully completed. Comparing with statistical information on hospital admissions, the study appears to have captured information from at least 70 percent of all admitted children during the study periods, which supports that our data reflect paediatric drug use at Swedish hospitals in general [12]. Therefore, we believe that the study provides a good estimation of the current drug use by children at Swedish hospitals.

It cannot be excluded that the high use of EPD morphine and glucose found in study **IV** could be slightly overestimated, due to unclear documentation in the prescription form. Some of these EPD prescriptions could have been licensed drugs that had been diluted by the health care provider, which still would correspond to *off-label* drug use for morphine.

5.4 Future studies and challenges

The extensive collection of data in our last study on drug treatment to children at Swedish hospitals (**IV**) allows for several in-depth studies on different age groups and/or different therapeutic areas. Primarily, a study of the drugs prescribed to premature infants is planned. Other studies that are planned are a deeper investigation of EPD and unlicensed drugs, as well as calculations of defined daily dosages for certain drugs.

To improve the documentation on drug efficacy and safety in children, attempts have been made by medical authorities (US Food and Drug Administration and European Medical Agency) to stimulate drug industry to perform paediatric clinical trials and submit paediatric labelling information [97, 98]. These attempts have included some economic incentives regarding patent protection [97] for both newly authorised drugs [99] and drugs already on the market [100]. However, it will take several years before these initiatives will have a large impact on the paediatric documentation of drugs in general. Study **IV** was performed as part of a pan-European effort, organised via EMA, to collect data on the current situation of paediatric drug use and prescribing. These data are meant to serve as a basis for the allocation of economic incentives to the medical academia to perform studies on the efficacy and safety of drugs that are of special concern in the paediatric population, which is in process.

There are numerous examples of ambiguity of, or inappropriate and inconsistent descriptions of paediatric information in the SPC texts. For example, omeprazole tablets and esomeprazole oral formulas are on-label for paediatric use, whereas the intravenous administration form is *off-label*. In many SPCs, it is also mentioned that a certain drug should not be given to children or can be given to children, without any further definition of any age limits. Thus, an important issue concerning *off-label* drug use in the paediatric population is to harmonise the paediatric labelling regarding

administration forms, age definitions and between drugs from different drug manufacturers. Regulatory authorities could also guide manufacturers to avoid recommendations that e.g. suppositories or tablets should be divided several times to children. Thus, they would also support the production and availability of more appropriate administration forms for the youngest patients. It would also improve the documentation of paediatric drug treatment if the approval process and design of SPC was based on the patient's needs rather than economic interests.

Although harmonization and clarifications of the SPC would be a great improvement, the information also needs to be made readily available to the prescribers, preferably through computerized clinical decision support system. In such a system, evaluated clinical documentation and scientific data, in addition to SPC information, could be presented to the prescriber in an easily accessible way at the moment of prescribing.

The lack of scientific documentation concerning drug safety and efficacy in children also applies to OTC drugs and herbal remedies. It has been suggested that children are subject to substantial self-medication by their guardians with these types of pharmaceuticals [48]. Greater efforts and resources should be devoted to research in this area, primarily to evaluate the possible hazardous effects in children and develop surveillance network for paediatric drug treatment.

6 CONCLUSIONS

Off-label drug prescribing to paediatric patients is substantial, both in primary and hospital health care, and must be regarded as a patient safety issue.

Off-label prescribing was a common phenomenon among drugs reported to have caused an ADR in paediatric outpatients, and was more often found in serious than non-serious ADR reports.

The most vulnerable paediatric group, neonates and infants, have the highest exposure of drugs given at hospitals in an *off-label* manner, as well as extemporaneously prepared and unlicensed drugs.

Off-label paediatric drug prescribing remains a public health concern and further clinical trials in children, as well as more focused interventions, such as careful post-marketing surveillance of drug safety are needed.

A harmonization of SPC texts with regard to the structure of the paediatric information, to available scientific evidence, to differing information between drug manufactures, and to inconsistencies between e.g. different administration routes is also urgently needed, and would greatly reduce the degree of *off-label* drug use in children.

Other sources of information, besides the SPCs, are also needed to ensure safe and effective drug treatment in children, such as Drug Information Centres, dedicated Drug and Therapeutic Committees and clinical decision support systems.

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